

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification⁶ : A61K 31/155, 47/12, 47/26</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/55320 (43) International Publication Date: 4 November 1999 (04.11.99)</p>
<p>(21) International Application Number: PCT/JP99/02192 (22) International Filing Date: 26 April 1999 (26.04.99) (30) Priority Data: 10/136126 29 April 1998 (29.04.98) JP (71) Applicant (for all designated States except US): SUMITOMO PHARMACEUTICALS CO., LTD. [JP/JP]; 2-8, Doshomachi 2-chome, Chuo-ku, Osaka-shi, Osaka 541-8510 (JP). (72) Inventors; and (75) Inventors/Applicants (for US only): NISHII, Hiroyuki [JP/JP]; 9-1-404, Tamagawa 1-chome, Takatsuki-shi, Osaka 569-0857 (JP). KOBAYASHI, Hirohisa [JP/JP]; 12-10, Nakatsu-cho, Ibaraki-shi, Osaka 567-0824 (JP). OTODA, Kazuya [JP/JP]; 1-10, Nakayama-sakuradal 5-chome, Takarazuka-shi, Hyogo 665-0877 (JP). (74) Agent: NAKAMURA, Toshio; Sumitomo Pharmaceuticals Co., Ltd., Intellectual Property Dept., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi, Osaka 554-0022 (JP).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID (57) Abstract An oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness.</p>		

A03

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

DESCRIPTION

ORAL FORMULATION COMPRISING BIGUANIDE AND AN ORGANIC ACID

5 TECHNICAL FIELD

The present invention relates to an oral fomulation comprising a biguanide and an organic acid.

BACKGROUND OF THE INVENTION

10 Biguanides such as metformin have unpleasant tastes such as bitterness and saltiness. The dosages of metformin are about 250 mg per dose in Japan and about 850 mg per dose in United States of America. In spite of such big dosages, only tablets are on sale at present.

15 There are several known methods for masking bitterness of bitter drugs, for instance, for solid formulations, sugar coated tablets, film coated tablets, capsules and the like are useful. Powders, fine granules and granules are formulated with sweetening agents or flavors; microcapsules, non-enteric coated formulation, 20 spray-dried formulation with low melting point wax, formulation with lecithin (JP 62-265234-A) and the like may also be used. For solutions, there are formulations with water-insoluble high molecular weight compound such as ethylcellulose and hydroxypropylmethylcellulose phthalate (JP 52-41214-A); formulations 25 with acidic phospholipids or lyso-phospholipids (JP 7-67552-A); and formulations with a large amount of citric acid (JP 4-58452-B).

DISCLOSURE OF THE INVENTION

The inventors of the present invention have intensively carried

out research, and found that an oral formulation comprising a biguanide and an organic acid has less unpleasant tastes such as bitterness and saltiness. Thus, the present invention has been accomplished.

5

The present inventions includes:

[1] An oral formulation comprising a biguanide and an organic acid.

10 [2] An oral formulation comprising a biguanide, an organic acid and a sweetening agent.

[3] An oral formulation according to [1] or [2] wherein the biguanide is metformin or a pharmaceutical salt thereof.

15 [4] An oral formulation according to any one of [1] to [3] wherein the organic acid is malic acid, citric acid, tartaric acid or mixture thereof.

[5] An oral formulation according to any one of [1] to [4] wherein the sweetening agent is aspartameTM, saccharine, saccharine sodium, stevioside or mixture thereof.

20 [6] An oral formulation according to any one of [1] to [5] wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.

[7] An oral formulation according to any one of [2] to [6] wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10

25 [8] An oral formulation according to any one of [1] to [7] wherein the formulation is solution, jelly, gum drops, dry syrup, powders, fine granules or granules.

[9] An oral formulation according to any one of [1] to [8] wherein the pH of the solution is 3.5 to 6 in case that the

formulation is solution, and the pH of the solution which is formed by dissolving or dispersing the formulation to 10 times more (w/w) volume of water, is 3.5 to 6 in case that the formulation is not solution.

5

DETAILED DESCRIPTION OF THE INVENTION

"Biguanide" includes compounds having a biguanide structure such as metformin, buformin, fenformin and pharmaceutically acceptable salts thereof.

10

"Organic acid" includes malic acid, citric acid, tartaric acid, ascorbic acid, succinic acid, fumaric acid, maleic acid, gluconic acid, glucuronic acid and mixtures thereof. Preferable organic acids are organic acids having 2 or 3 carboxyl groups such as malic acid, citric acid and tartaric acid, more preferably malic acid.

15

The ratio (w/w) of the biguanide to the organic acid is, for example, 1 : 0.01 to 1 : 50, preferably 1 : 0.02 to 1 : 10, more preferably 1 : 0.05 to 1 : 1. In the case of malic acid, the preferable ratio (w/w) of the biguanide to malic acid is 1 : 0.05 to 1 : 0.5.

20

"Sweetening agent" includes aspartameTM, saccharin, saccharin sodium, stevioside, *sormatin*, erythritol, sorbitol, xylitol, glycerin and mixtures thereof. Preferable sweetening agents are aspartameTM, saccharin, saccharin sodium and stevioside. The ratio (w/w) of the biguanide to the sweetening agent is, for example, 1 : 0.001 to 1 : 10, preferably 1 : 0.02 to 1 : 1.

25

When the formulation is a solution, preferably the pH of the solution is 3.5 to 6, more preferably 4 to 6, to decrease the unpleasant tastes and to keep the biguanide stable. If the formulation is not a solution, the preferable pH of the solution or

dispersion which is formed by dispersing the formulation in water (1 part of the formulation to 10 parts of water, by weight), is 3.5 to 6, more preferably 4 to 6; This is in order to decrease the unpleasant tastes and to keep the biguanide stable.

5

"Oral formulation" includes solution, jelly, gum drops, dry syrup, powders, fine granules and granules. Preferably the formulation is not in the form of tablets.

10

The formulation of the present invention may include pharmaceutically acceptable non-toxic and inactive additives. Additives include excipients such as corn starch, potato starch, white sugar, mannitol, xylitol, sorbitol, talc, kaolin, calcium monohydrogen phosphate, calcium sulfate, calcium carbonate, crystalline cellulose; lubricants such as magnesium stearate and potassium stearate; disintegrators such as carboxymethylcellulose calcium and low substituted hydroxymethylcellulose; binders such as hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, gelatin, methylcellulose, Arabia gum and polyvinylalcohol; coloring agents; correctives; adsorbents; preservatives; stabilizers; moistening agents; de-charging agents; pH adjusters; and the like.

15

20

25

The formulation may include flavors such as lemon, orange, grapefruit, pine, banana, chocolate and yogurt to decrease the unpleasant tastes more.

The formulation of the present invention can be prepared by well known methods. In the case of solid formulations, the formulation can be prepared, for example, by extruding granulation

methods, crushing granulation methods, dry granulation methods, fluidized bed granulation methods, tumbling granulation methods, high shear mixing granulation methods, wet compression methods, direct compression methods and the like.

5

The formulation of the present invention will contain the conventional amounts of active ingredient (biguanide) and will be used in conventional manner to administer doses in accordance with normal practice by routes and according to dosage regimes which are familiar to pharmacologists and medical practitioners.

10

The present invention will be described in detail below, referring to Examples and Experiments, which are not limitative of the present invention.

15

Example 1

Solution of metformin hydrochloride

	Ingredient	weight %

20	Metformin hydrochloride	5 %
	Malic acid	0.8 %
	Aspartame TM	0.3 %
	Lemon flavor	0.1 %
	Purified water	93.8 %

25

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartameTM and lemon flavor into purified water.

Example 2

Solution of metformin hydrochloride

	Ingredient	weight %

	Metformin hydrochloride	5 %
5	Malic acid	0.8 %
	Saccharin sodium	1 %
	Lemon flavor	0.1 %
	Purified water	93.1 %

5 % Solution of metformin hydrochloride is prepared by
10 dissolving metformin hydrochloride, malic acid, saccharine sodium
and lemon flavor into purified water.

Example 3

Solution of metformin hydrochloride

15	Ingredient	weight %

	Metformin hydrochloride	5 %
	Citric acid	2 %
	Aspartame TM	0.3 %
20	Lemon flavor	0.1 %
	Purified water	92.6 %

5 % Solution of metformin hydrochloride is prepared by
dissolving metformin hydrochloride, citric acid, aspartameTM and
lemon flavor into purified water.

25

Example 4

Solution of metformin hydrochloride

Ingredient	weight %

	Metformin hydrochloride	5 %
	Malic acid	1.5 %
	Saccharin sodium	0.25 %
	Erythritol	10 %
5	Lemon flavor	0.1 %
	Purified water	83.15 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, erythritol and lemon flavor into purified water.

10

Example 5

Solution of metformin hydrochloride

	Ingredient	weight %

15	Metformin hydrochloride	5 %
	Malic acid	1.5 %
	Aspartame TM	0.2 %
	Sorbitol	6 %
	Grapefruit flavor	0.1 %
20	Purified water	87.2 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, aspartameTM, sorbitol and grapefruit flavor into purified water.

25 Example 6

Solution of metformin hydrochloride

	Ingredient	weight %

	Metformin hydrochloride	5 %

	Malic acid	1.5 %
	Saccharin	0.03 %
	Glycerin	10 %
	Lemon flavor	0.1 %
5	Purified water	83.37 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin, glycerin and lemon flavor into purified water.

10 Example 7

Solution of metformin hydrochloride

	Ingredient	weight %

	Metformin hydrochloride	5 %
15	Malic acid	1.5 %
	Saccharin sodium	0.25 %
	Saccharin	0.03 %
	Lemon flavor	0.1 %
	Purified water	93.12 %

20 5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride, malic acid, saccharin sodium, saccharin and lemon flavor into purified water.

Example 8

25 Dry syrup of metformin hydrochloride

	Ingredient	Amount

	Metformin hydrochloride	500 g
	Malic acid	80 g

Saccharin sodium	25 g
Erythritol	865 g
Polyvinylpyrrolidone K30	30 g

5 Total 1500 g

Metformin hydrochloride, malic acid, saccharin sodium, erythritol and polyvinylpyrrolidone K30 are mixed with 200 g of mixture of purified water and ethanol (1 : 1 (w/w)) to give wet solid. 33 % Dry syrup of metformin hydrochloride is prepared by
10 milling the wet solid with a granulation mill to adjust the size of the granules, followed by drying.

Example 9

Jelly of metformin hydrochloride

15	Ingredient	weight %

	Metformin hydrochloride	5 %
	Gelatin	0.5 %
	Malic acid	0.8 %
20	Aspartame TM	0.3 %
	Lemon flavor	0.1 %
	Purified water	93.3 %

Jelly of metformin hydrochloride is prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartameTM and
25 lemon flavor into gelatin solution which is made by dissolving gelatin to purified water over 80 °C, followed by cooling.

Example 10

Fine granules of buformin hydrochloride

	Ingredient	Amount
	-----	-----
	Buformin hydrochloride	100 g
	Mannitol	300 g
5	Lactose	300 g
	Corn starch	150 g
	Malic acid	90 g
	Aspartame TM	30 g
	Methylcellulose	30 g
10	-----	-----
	Total	1000 g

Buformin hydrochloride, mannitol, lactose, corn starch, malic acid, aspartameTM and methylcellulose are mixed with 200 g of purified water to give wet solid. 10 % Fine granules of buformin hydrochloride are prepared by granulating the wet solid with a basket granulation mill, followed by drying.

Example 11

Gum drops of buformin hydrochloride

20	Ingredient	Amount
	-----	-----
	Buformin hydrochloride	100 mg
	Gelatin	600 mg
	Citic acid	100 mg
25	Saccharin sodium	25 mg
	Sorbitol	1550 mg
	Lemon flavor	25 mg
	Purified water	600 mg
	-----	-----

Total 3000 mg

Gum drops of buformin hydrochloride are prepared by dissolving or dispersing buformin hydrochloride, citric acid, saccharin sodium, sorbitol and lemon flavor into gelatin solution which is made by dissolving gelatin to purified water over 80 °C, followed by molding the mixture and cooling.

Example 12

Powders of buformin hydrochloride

10	Ingredient	Amount

	Buformin hydrochloride	100 mg
	Mannitol	560 mg
	Corn starch	200 mg
15	Citric acid	100 mg
	Aspartame TM	30 mg
	Magnesium stearate	10 mg

	Total	1000 mg

20 10 % powders of buformin hydrochloride are prepared by mixing buformin hydrochloride, mannitol, corn starch, citric acid, aspartameTM and magnesium stearate.

Example 13

25 Solutions of metformin hydrochloride at various pH

Using the same amount of each ingredient of Example 1, 5 % solutions of metformin hydrochloride at various pH are prepared by dissolving or dispersing metformin hydrochloride, malic acid, aspartameTM and lemon flavor into about 80 % of purified water.

followed by adjusting pH of the solution to pH 2, 3, 3.5, 4, 5 or 6 using dilute hydrochloric acid or dilute sodium hydroxide solution and adding more purified water.

5 Reference example 1

Solution of metformin hydrochloride

	Ingredient	weight %

	Metformin hydrochloride	5 %
10	Purified water	95 %

5 % Solution of metformin hydrochloride is prepared by dissolving metformin hydrochloride into purified water.

Experiment 1

15 Tasting experiment

Tasting experiments on the solutions of Examples 1 to 3 and Reference example 1 were carried out with 20 panelists. The numbers of panelists who felt the solution "not bitter", "a little bitter" and "very bitter" are shown in Table 1.

20 Table 1

	Solution	"not bitter"	"a little bitter"	"very bitter"

	Example 1	11	8	1
	Example 2	10	9	1
25	Example 3	11	8	1
	Reference example 1	0	2	18

Tasting experiments on the solutions of Examples 4 to 7 were also carried out, with satisfactory results.

Experiment 2

Tasting and stability experiments

Tasting and stability experiments on the solutions at various pH of Example 13 were carried out, in the same manner as Experiment 1. A stability experiment was carried out by measuring the remaining amount of metformin in the solutions with HPLC after heating the solutions in vials at 60 °C for 2 weeks. The results are shown in Table 2.

Table 2

	pH	taste	remaining amount(%)
	2	very sour	78
15	3	sour	86
	3.5	good	94
	4	good	96
	5	good	98
	6	good	100
20	7	very bitter	98

Metformin hydrochloride is not stable below pH 3.5, and the solution tastes sour. The solution over pH 7 has bitterness.

Normally we feel bitterness most in solution formulation. Therefore these experiments on the solutions indicate that other formulations such as jelly, gum drops, dry syrup, powders, fine granules and granules have less unpleasant tastes as well.

The present invention provides an oral formulation of biguanide with less unpleasant tastes. With this invention, people in every age group, for example, elderly people and little children can easily have sufficient amount of biguanide.

CLAIMS

1. An oral formulation comprising a biguanide and an organic acid.
- 5 2. An oral formulation comprising a biguanide, an organic acid and a sweetening agent.
3. An oral formulation according to Claim 2 wherein the sweetening agent is selected from aspartameTM, saccharine, saccharine sodium, stevioside and mixtures thereof.
- 10 4. An oral formulation according to Claim 2 or Claim 3 wherein the ratio (w/w) of the biguanide to the sweetening agent is 1 : 0.001 to 1 : 10
5. An oral formulation according to any one of Claims 1 to 4 wherein the biguanide is metformin or the pharmaceutical salt
- 15 thereof.
6. An oral formulation according to any one of Claims 1 to 5 wherein the organic acid is selected from malic acid, citric acid, tartaric acid and mixtures thereof.
7. An oral formulation according to any one of Claims 1 to 6
- 20 wherein the ratio (w/w) of the biguanide to the organic acid is 1 : 0.01 to 1 : 50.
8. An oral formulation according to any one of Claims 1 to 7 in the form of a solution, jelly, gum drops, dry syrup, powders, fine granules or granules.
- 25 9. An oral formulation according to Claims 8 which is in the form of a solution wherein the pH of the solution is 3.5 to 6.
10. An oral formulation according to Claims 8 which is not in the form of a solution and the pH of the solution or dispersion which is formed by dispersing 1 part of the formulation in 10 parts

by weight of water is 3.5 to 6.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 99/02192

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/155 A61K47/12 A61K47/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 21 24 256 A (DR. CHRISTIAN BRUNNENGRÄBER) 30 November 1972 (1972-11-30) page 4; example 1 ---	1
Y	GB 1 539 076 A (MEIJI SEIKA KAISHA) 24 January 1979 (1979-01-24) page 1, right-hand column, line 19-33 page 4; example 6 ---	1-10
Y	EP 0 390 369 A (AMERICAN HOME PROD) 3 October 1990 (1990-10-03) claims 1,2 --- -/--	1-10



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 August 1999

Date of mailing of the international search report

13/08/1999

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Herrera, S

INTERNATIONAL SEARCH REPORT

Intern. Appl. Application No

PCT/JP 99/02192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 010, no. 120 (C-343), 6 May 1986 (1986-05-06) & JP 60 246325 A (TAKEDA YAKUHI KOGYO KK), 6 December 1985 (1985-12-06) abstract -----	1-10
P, A	WO 98 27982 A (ICHIHARA JUNJI ;ITAKURA YASUSHI (JP); NOGUCHI HIROSHI (JP); SUMITO) 2 July 1998 (1998-07-02) -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 99/02192

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2124256 A	30-11-1972	NONE	
GB 1539076 A	24-01-1979	JP 1209258 C	29-05-1984
		JP 52041214 A	30-03-1977
		JP 58040529 B	06-09-1983
		BE 838239 A	28-05-1976
		CA 1069047 A	31-12-1979
		DE 2604044 A	31-03-1977
		FR 2325388 A	22-04-1977
		NL 7601069 A,B,	31-03-1977
		SE 418146 B	11-05-1981
		SE 7601096 A	30-03-1977
		US 4101651 A	18-07-1978
EP 0390369 A	03-10-1990	US 4975465 A	04-12-1990
		AT 100313 T	15-02-1994
		AU 629622 B	08-10-1992
		AU 5226990 A	04-10-1990
		CA 1336819 A	29-08-1995
		DE 69006068 D	03-03-1994
		DE 69006068 T	11-05-1994
		DK 390369 T	11-04-1994
		ES 2048428 T	16-03-1994
		HK 68194 A	22-07-1994
		IE 64024 B	28-06-1995
		JP 2286615 A	26-11-1990
		JP 2847134 B	13-01-1999
		KR 143899 B	15-07-1998
		MX 20055 A,B	01-10-1993
JP 60246325 A	06-12-1985	JP 1948417 C	10-07-1995
		JP 4058452 B	17-09-1992
WO 9827982 A	02-07-1998	NONE	